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The effects of vitamin D supplementation on airway functions in mild to moderate persistent asthma

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ABSTRACT

Background: Vitamin D is hypothesized to have some roles in innate and adaptive immunity, inflammation reduction, and remodeling; therefore, it is supposed to affect the asthma phenotype, severity, and response to inhaled corticosteroid (ICS).
Objective: To explore the synergistic effects of vitamin D supplementation in addition to asthma controllers (ICS or ICS plus long-acting β-agonist) on airway functions.
Methods: A randomized clinical trial was conducted in 130 individuals aged 10 to 50 years who lived in Tehran during a 24-week period. Data on age, sex, body mass index, stage of asthma, serum total IgE, history of allergic rhinitis, atopic dermatitis, food allergy, and urticaria were collected. Spirometric parameters (forced expiratory volume in 1 second [FEV_1] and ratio of FEV_1 to forced vital capacity) and serum vitamin D measurement were obtained before and 8 and 24 weeks after the intervention. Patients were divided in 2 groups randomly. Both groups received asthma controllers (budesonide or budesonide plus formoterol) according to their stage, but the intervention group received vitamin D supplementation (100,000-U bolus intramuscularly plus 50,000 U orally weekly) in addition to asthma controllers.
Results: FEV_1 improved significantly in both groups after 8 weeks, but no significant difference was found between the 2 groups at baseline ($P = .20$) or after 8 weeks ($P = .99$); however, a significant improvement was seen in the intervention group in the last 16 weeks, and FEV_1 was significantly better in the intervention group than the other group after 24 weeks ($P < .001$).
Conclusion: Vitamin D supplementation associated with asthma controllers could significantly improve FEV_1 in mild to moderate persistent asthma after 24 weeks.
Trial Registration: irct.ir Identifier: IRCT201302079608N1.

Introduction

There are no clear reasons for the increased prevalence of allergic diseases, especially asthma, in recent decades.[1,2] Some epidemiologic studies suggest that vitamin D deficiency is associated with an increased incidence of asthma symptoms.[3,4] Vitamin D has a critical role in corticosteroid resistance in asthma, suggesting that vitamin D may play a role in the control of asthma.[5] Some studies suggest that vitamin D interacts with glucocorticoid signaling pathways[5] and supplementation with the active pharmacologic form of vitamin D_3 enhances dexamethasone-induced expression of interleukin (IL) 10 by T-regulatory cells.[6] It has been already reported that vitamin D has several effects on the innate and adaptive immune system that might be relevant to asthma morbidity.[7–10] A number of studies have concluded that low 25-hydroxy-vitamin D in mild to moderate asthma is correlated with poor asthma control, reduced lung function, reduced glucocorticoid response, more frequent exacerbations, and increased corticosteroid use.[10–12] Even though there are sufficient basic and epidemiologic studies to support a causal relationship between vitamin D and asthma, clinical data that address the effect of vitamin D supplementation on disease control and severity are limited in asthma patients. Therefore, the aim of this clinical trial

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was to investigate the synergistic role of vitamin D supplementation on airway functions in addition to standard asthma treatment.

Methods

This prospective, randomized, open-label, active controlled clinical trial was designed in an outpatient setting, and patients with mild to moderate persistent asthma 10 to 50 years old were enrolled according to inclusion and exclusion criteria. Rasool-e-Akram is a referral hospital in Tehran, and the study participants were selected from patients visited in the allergy or pulmonology clinics of the hospital. Because some interventional factors, such as skin pigmentation, diet, sun exposure level, and clothing habits, can affect vitamin D metabolism, only native Fars patients living in Tehran were selected, so our patients had minimal difference in skin color.

However, we did not check their dietary intake of vitamin D. The main inclusion criteria were a diagnosis of mild to moderate persistent asthma according to the Global Initiative for Asthma 2012,[13] age of 10 to 50 years, and consent to participate in this study. Exclusion criteria were a diagnosis of chronic obstructive pulmonary disease,[14] known sarcoidosis, hyperparathyroidism, nephrolithiasis, active tuberculosis, vitamin D intolerance, liver failure, renal failure, lymphoma or other malignant tumors not in remission for more than 2 years,[15,16] treatment with anticonvulsants, vitamin D supplementation, systemic corticosteroid therapy up to 3 months before or during the study,[17] breastfeeding or pregnancy, baseline serum calcium level greater than 2.65 mmol/L, asthma exacerbation 3 months before or during the study, active or passive smoking, and incomplete use of asthma controller drugs during the study. One hundred sixty individuals were selected during routine visits in our clinic based on the outlined criteria, but only 130 patients participated once they were notified of beginning the study (64 in the intervention group and 66 in the control group) and 30 patients did not participate in the study at the time of notification. All participants were notified at the same time in April 2013. Using consecutive random selection, the participants were divided in 2 groups of intervention and control. Spirometry and serum 25-hydroxy-vitamin D level was measured before and 8 and 24 weeks after the study. Spirometry was performed in accordance with American Thoracic Society recommendations[18] in the allergy clinic of Rasool-e-Akram Hospital using JAEGER (Jaeger, Master Screening PAED, Hoechburg, Germany) and the best forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were recorded.

The serum level of 25-hydroxy-vitamin D was measured by radioimmunoassay[19] using 25-hydroxy-vitamin D enzyme immunoassay (AC-57F1.ids.UK). Spirometry, vitamin D measurement, and determination of level of asthma control were performed at 0, 8, and 24 weeks. Fifteen patients were lost to follow-up during the first 8 weeks (6 patients in the intervention group and 9 in the control group), and 7 patients were lost to follow-up during the next 16 weeks (3 in the intervention group and 4 in the control group). During the first 8 weeks, 7 patients were excluded because of asthma exacerbation (4 in the intervention group and 3 in the control group), 6 patients were excluded because of poor adherence (2 in the intervention group and 4 in the control group), and 2 patients were excluded because of stepping up to the severe persistent level. In the next 16 weeks, 7 patients were lost to follow-up (3 in the intervention group and 4 in the control group), which was due to poor adherence without changing the level of asthma treatment; therefore, a total of 108 patients completed the study (Fig 1). Adherence to vitamin D and asthma controller drug was evaluated on the basis of weekly follow-up through telephone calls. Budesonide alone or budesonide plus formoterol both in the form of dry powder inhaler were prescribed after adjustment according the stage of asthma. Patients in the intervention group received a bolus dose of 100,000 U of vitamin D intramuscularly followed by 50,000 U of oral vitamin D pearls on a weekly basis.[20–22] No serious adverse reactions or adverse effects were noticed during vitamin D supplementation.

The study was approved by the Ethics Committee and was registered at www.irct.ir (Identifier IRCT201302079608N1). The patients were informed about the aim of the study and were instructed on how to use a dry powder inhaler. Moreover, an informed consent form was consequently signed by each participant. Efficacy was assessed using intent-to-treat analyses. Numeric and categorical variables were described with mean (SD) and relative frequency, respectively. We used paired-samples *t* tests and independent-samples *t* tests to compare mean numeric variables

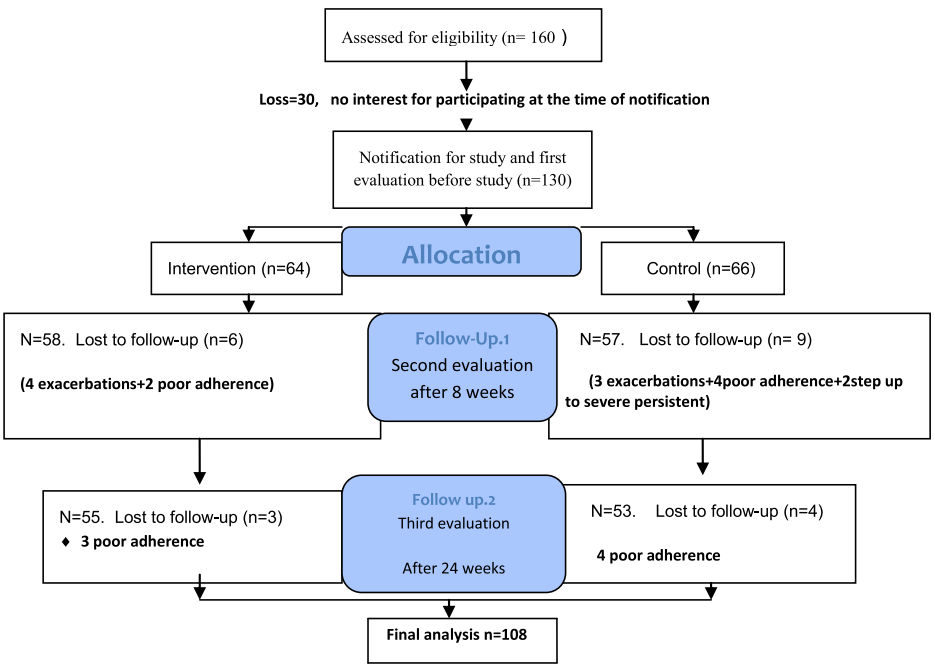

Figure 1. Algorithm of the study.

Table 1
Characteristics of the study participants before the study

Characteristic	Intervention group (n = 64)	Control group (n = 66)	*P* value
Age, mean (range), y	24.40 (10.5–49.0)	28.64 (10.0–49.1)	.25
BMI	23.04 (16.5–35.5)	24.09 (15.64–38.0)	.88
Female, %	57.8	63.6	.49
Male, %	42.2	36.4	
Mild persistent asthma, No. (%)	33 (51.6)	39 (59.1)	.87
Moderate persistent asthma, No. (%)	31 (48.4)	27 (40.9)	
IgE level, IU/mL	133.15 (11–409)	120.19 (8–492)	.32
Allergic rhinitis, No. (%)	37 (57.8)	38 (57.6)	.95
Atopic dermatitis, No. (%)	16 (25.0)	14 (21.2)	.31
Urticaria, No. (%)	9 (14.3)	10 (15.4)	.72
Food allergy, No. (%)	12 (18.8)	6 (9.2)	.82
Vitamin D level before study, ng/mL	23.82 (5.4–70.7)	24.02 (5.4–71.2)	.93

Abbreviation: BMI, body mass index.

within and across groups, respectively. The χ^2 test was used to compare relative frequency between groups. The level of significant was considered .05. All analyses were performed with SPSS statistical software, version 16 (SPSS Inc, Chicago, Illinois).

Results

A total of 130 patients who met the inclusion criteria were enrolled in this study and were randomly assigned to intervention and control groups. Age, sex, body mass index (BMI), stage of asthma (mild persistent or moderate persistent), history of atopic dermatitis, allergic rhinitis, food allergy or urticaria, serum total IgE, FEV_1, ratio of FEV_1 to forced vital capacity (FVC), and serum vitamin D were considered as variables for final analysis. Of 130 enrolled patients, 72 cases (55.4%) had mild persistent asthma, and 58 cases (44.6%) had moderate persistent asthma. The mean (SD) vitamin D level was 23.5 (18.4) ng/mL in patients with mild persistent asthma and 24.4 (17.5) ng/mL in patients with

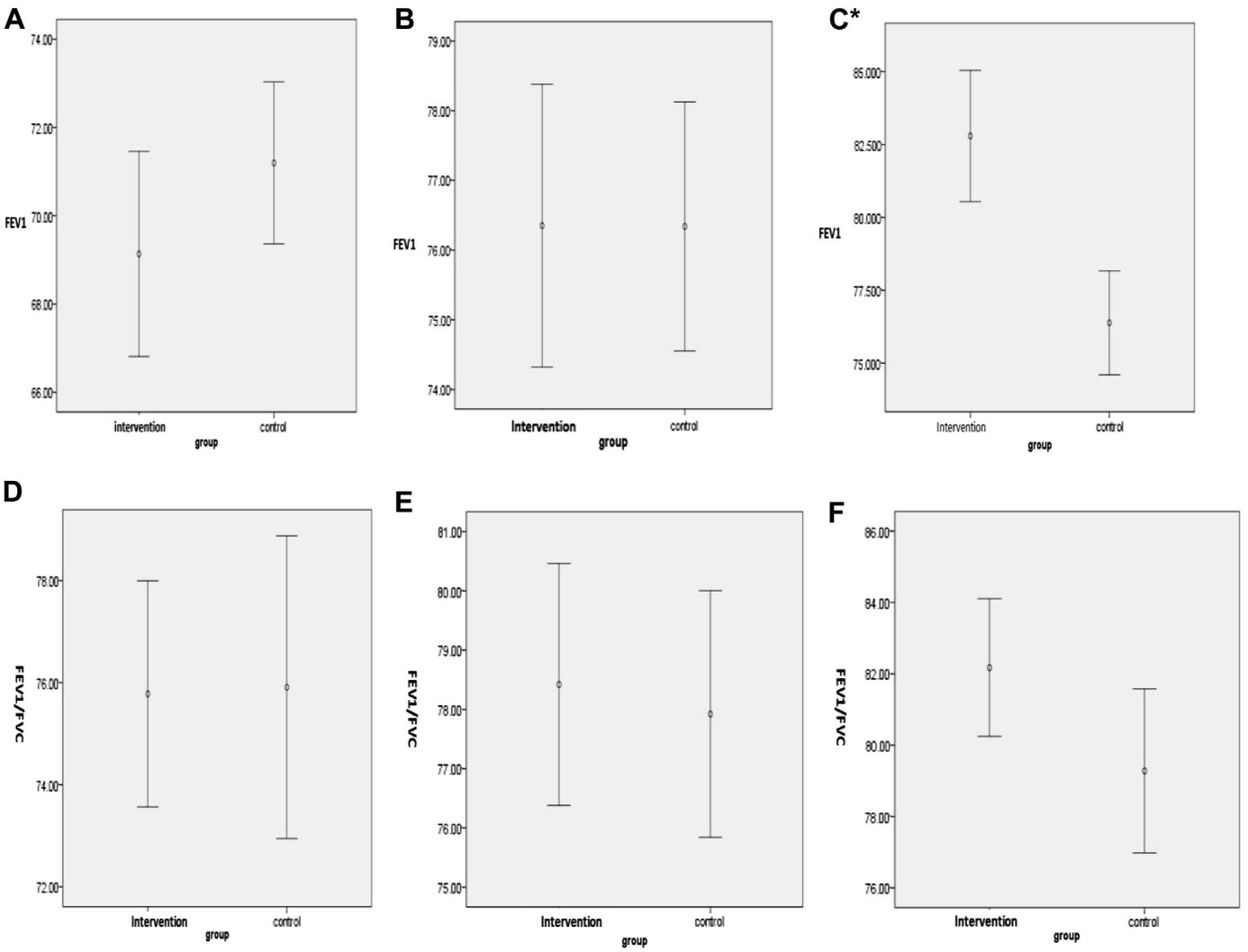

Figure 2. *A*, Forced expiratory volume in 1 second (FEV_1) before study ($P = .16$). *B*, FEV_1 after 8 weeks ($P = .99$). *C*, FEV_1 after 24 weeks ($^*P < .001$). *D*, Ratio of FEV_1 to forced vital capacity (FVC) before study ($P = .94$). *E*, FEV_1/FVC ratio after 8 weeks ($P = .73$). *F*, FEV_1/FVC ratio after 24 weeks ($P = .06$). $^*P < .05$ indicate statistical significance.

moderate persistent asthma without any significant difference ($P = .77$). Demographic data of the patients are presented in Table 1. No significant differences were observed between 2 groups before the study. FEV_1 had a significant improvement after 8 weeks in both groups ($P < .001$ in the intervention group and $P = .001$ in the control group), but there was no significant difference between the 2 groups at the 8-week analysis ($P = .16$) (Fig 2). During the next 16 weeks, between 8 and 24 weeks, the FEV_1 significantly improved only in the intervention group with no significant change in the control group ($P < .001$ in the intervention group and $P = .64$ in control group). In final analysis at week 24, the FEV_1 was significantly higher in the intervention group ($P < .001$) (Fig 2). The FEV_1/FVC ratio had a significant improvement after 8 and 24 weeks in the intervention group ($P = .002$ after 8 weeks and $P < .001$ after 24 weeks), whereas the improvement was significant only after 24 weeks in the control group ($P = .48$ after 8 weeks and $P = .001$ after 24 weeks). The FEV_1/FVC ratio did not reveal a significant difference between the 2 groups at 8 and 24 weeks ($P = .73$ after 8 weeks and $P = .06$ after 24 weeks) (Fig 2). There was a positive correlation between serum vitamin D and FEV_1 before the study in all patients ($P = .001$, $r = 0.272$); however, after 8 weeks of treatment, this rhythm had a negative correlation between vitamin D and FEV_1 without any significant difference ($P = .25$, $r = -0.063$), but after 24 weeks there was again a positive correlation between serum vitamin D level and FEV_1 with a significant difference ($P < .001$, $r = 0.336$). The correlation between Δ vitamin D and Δ FEV_1 was also measured after 8 ($r = 0.092$, $P = .33$) and 24 ($r = 0.543$, $P < .001$) weeks (Fig 3, C and D). FEV_1 and vitamin D level changes during the study are shown in Figure 3, A and B, for each group.

Discussion

Long-term inhaled corticosteroids are the main asthma controllers; however, a substantial proportion of patients do not achieve optimal asthma control despite high-dose treatment.[23] In addition, many of the patients are prone to recurrent exacerbations because of common respiratory viral infections.[2] Vitamin D is required for fetal lung development.[24] It interacts with glucocorticoid signaling pathways.[5] Investigations have found that vitamin D_3 can induce expression of interleukin 10 by T-regulatory cells[6] and block smooth muscle proliferation in a concentration-dependent manner in human smooth muscle, both of which are outlined in asthma pathogenesis.[25] Furthermore, vitamin D has multiple cytokine modulatory effects.[26,27] Vitamin D increases the production of cathelicidine in macrophages and has a beneficial effect on the clearance of infections.[28–31]

Recent publications indicate that maternal intake of vitamin D during pregnancy leads to a decreased risk of recurrent wheezing in young children.[32,33] There are already many basic and epidemiologic surveys indicating the effect of vitamin D in asthma, but there are not enough trials. Yadav et al[34] found that 60,000 U of vitamin D monthly for 6 months, in addition to treating asthma, could reduce the asthma severity, number of exacerbations, corticosteroid use, emergency department visits, and peak expiratory flow rate.[34] Clifford and Knox[35] outlined different roles and mechanisms through which vitamin D may affect asthma, including variable adaptive and innate mechanisms. Despite the increasing evidence supporting the beneficial role of vitamin D in asthma treatment, there are still some controversies; for example, Ginde et al[36] reported that vitamin D supplementation

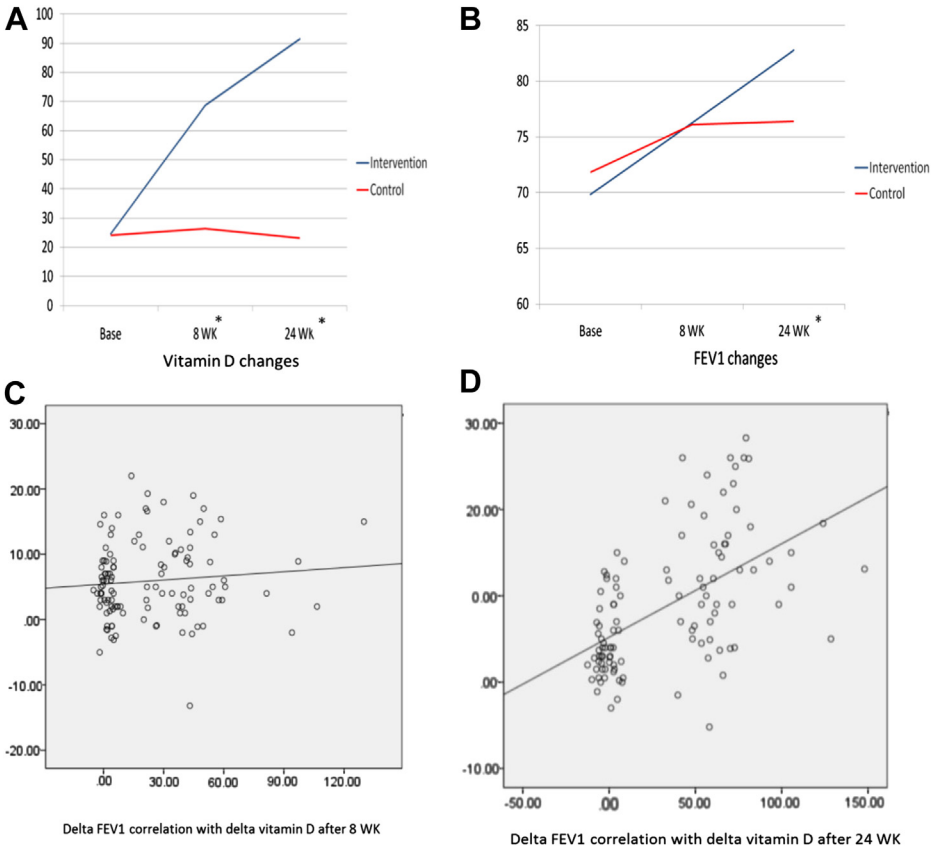

Figure 3. *A,* Vitamin D changes during study in each group. *B,* Forced expiratory volume in 1 second (FEV_1) changes during the study in each group. *C,* Correlation between Δ FEV_1 with Δ vitamin D after 8 weeks ($r = 0.092$, $P = .33$). *D,* Correlation between Δ FEV_1 with Δ vitamin D after 24 weeks ($r = .543$, $P < .001$). *$P < .05$ indicate statistical significance.

in the first year of life increased the risk of asthma by the age of 31 years; so, it is clear that more trials are needed to clarify any potential role of vitamin D as a therapeutic option for asthma treatment.

On the basis of these facts, the present study was designed to define the therapeutic role of vitamin D as an adjunct to asthma treatment. Varney et al[37] reported successful treatment of a difficult case of airway dysfunction syndrome that was resistant to inhaled corticosteroids with high-dose vitamin D. The patient's symptoms resolved at a vitamin D level of more than 150 nmol/L.[37] Because different functions of vitamin D (eg, bone mineral metabolism, immunologic, and secretory) appear in different serum levels and are dose dependent and there are suggestions that levels greater than 40 ng/mL are optimal for vitamin D immune functions[9,38,39] and considering the immunomodulatory aspects of vitamin D, we used high-dose vitamin D (100,000-U bolus plus 50,000 U weekly for 24 weeks) in our study, which was in the permitted range according to the literature.[20–22] After 8 weeks, the FEV_1 improved in both groups, which has expected because both groups used asthma controllers. There was no difference between the 2 groups after 8 weeks ($P = .99$). Vieth et al,[40] Lange et al,[41] and Di Rosa et al[42] explained the different immune modulatory aspects of vitamin D in different cells; however, it obviously takes time before they reach the appropriate concentration and exert their effects. Therefore, we believe that 8 weeks is not enough for this dose of vitamin D because vitamin D has its effects after 24 weeks. On the basis of the correlation between vitamin D and FEV_1, there was a negative rhythm between serum vitamin D and FEV_1 after the first 8 weeks of treatment ($r = -0.63$, $P = .25$), which we think can be explained by the run-in period needed for developing vitamin D immunologic effects; therefore, we believe that the improvement in the first 8 week in both groups was due to only asthma controller treatments.

During the next 16 weeks, FEV_1 did not improve significantly in the control group despite the regular use of asthma controllers, whereas FEV_1 improved significantly by continuing use of the controllers in the intervention group. In the end of study, there was a significant difference in FEV_1 between the 2 groups ($P < .001$), and interestingly there was a positive correlation between the vitamin D level and FEV_1 after 24 weeks with a significant difference ($P < .001$, $r = 0.366$).

Because of the significant difference in FEV_1 between the 2 groups ($P < .001$) after 24 weeks and the positive correlation ($r = 0.336$, $P < .001$) and the positive and significant correlation of Δ vitamin D and Δ FEV_1 only after 24 weeks ($r = 0.543$, $P < .001$), we hypothesize that the significant improvement in the 2 groups resulted from vitamin D supplementation.

This article could be more strengthened by writing a symptom score (Asthma Control Test or Asthma Control Questionnaire), but unfortunately it was not done. In addition, the small sample size (n = 130) of the study and the high mean BMI of the participants were the most important limitations of this study, although there was no significant difference in BMI between the both groups. We did not use placebo for parallel control, which was another limitation. We suggest further studies with larger sample sizes, stricter inclusion and exclusion criteria (eg, BMI), and use of placebo and different doses of vitamin D to determine the best effective dose of vitamin D. In conclusion, according to our findings, vitamin D supplementation may lead to a better and prolonged response to asthma controllers. For this purpose, it is better to use vitamin D for at least 24 weeks.

References

[1] Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med*. 2006;355:2226–2235.

[2] Sharifi L, Pourpak Z, Heidarnazhad H, Bokaie S, Moin M. Asthma knowledge, attitude, and self-efficacy in Iranian asthmatic patients. *Arch Iran Med*. 2011;14:315–320.

[3] Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? *J Allergy Clin Immunol*. 2007;120:1031–1035.

[4] Hypponen E, Sovio U, Wjst M, et al. Infant vitamin D supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. *Ann N Y Acad Sci*. 2004;1037:84–95.

[5] Xystrakis E, Kusumakar S, Boswell S, et al. Reversing the defective induction of IL-10–secreting regulatory T cells in glucocorticoid-resistant asthma patients. *J Clin Invest*. 2006;116:146–155.

[6] Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. *Am J Respir Crit Care Med*. 2010;181:699–704.

[7] Ginde AA, Sutherland ER. Vitamin D in asthma: panacea or true promise? *J Allergy Clin Immunol*. 2010;126:59–60.

[8] Paul G, Brehm JM, Alcorn JF, Holguin F, Aujla SJ, Celedon JC. Vitamin D and asthma. *Am J Respir Crit Care Med*. 2012;185:124–132.

[9] Brehm JM, Schuemann B, Fuhlbrigge AL, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol*. 2010;126:52–58.

[10] Goleva E, Searing DA, Jackson LP, Richers BN, Leung DY. Steroid requirements and immune associations with vitamin D are stronger in children than adults with asthma. *J Allergy Clin Immunol*. 2012;129:1243–1251.

[11] Brehm JM, Celedon JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med*. 2009;179:765–771.

[12] Wu AC, Tantisira K, Li L, Fuhlbrigge AL, Weiss ST, Litonjua A. The effect of vitamin d and inhaled corticosteroid treatment on lung function in children. *Am J Respir Crit Care Med*. 2012;186:508–513.

[13] Global Initiative for Asthma. GINA report, Global Strategy for Asthma Management and Prevention, revised 2012. www.ginasthma.org. Accessed July 28, 2015.

[14] Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013;187:347–365.

[15] Ralph AP. Vitamin D supplementation in patients with tuberculosis. *Am Fam Physician*. 2010;82:577–583.

[16] Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr*. 2007;85:6–18.

[17] Lee RH, Lyles KW, Colón-Emeric C. A review of the effect of anticonvulsant medications on bone mineral density and fracture risk. *Am J Geriatr Pharmacother*. 2010;8:34–46.

[18] American Thoracic Society. Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med*. 1995;152:1107–1136.

[19] Heijboer AC, Blankenstein MA, Kema IP, Buijs MM. Accuracy of 6 routine 25- hydroxyvitamin D assays: influence of vitamin D binding protein concentration. *Clin Chem*. 2012;58:543–548.

[20] Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr*. 2006;84:18–28.

[21] Vieth R, Bischoff-Ferrari H, Boucher BJ, et al. The urgent need to recommend an intake of vitamin D that is effective. *Am J Clin Nutr*. 2007;85:649–650.

[22] Maalouf J, Nabulsi M, Vieth R, et al. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. *J Clin Endocrinol Metab*. 2008;93:2693–2701.

[23] Korn S, Hübner M, Jung M, Blettner M, Buhl R. Severe and uncontrolled adult asthma is associated with vitamin D insufficiency and deficiency. *Respir Res*. 2013;14:25.

[24] Erkkola M, Kaila M, Nwaru BI, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy*. 2009;39:875–882.

[25] Gupta A, Sjoukes A, Richards D, et al. Relationship between serum vitamin d, disease severity, and airway remodeling in children with asthma. *Am J Respir Crit Care Med*. 2011;184:1342–1349.

[26] Bahar-Shany K, Ravid A, Koren R. Upregulation of MMP-9 production by TNF alpha in keratinocytes and its attenuation by vitamin D. *J Cell Physiol*. 2010;222:729–737.

[27] Searing DA, Leung DY. Vitamin D in atopic dermatitis, asthma and allergic diseases. *Immunol Allergy Clin North Am*. 2010;30:397–409.

[28] Gombart AF. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. *Future Microbiol*. 2009;4:1151–1165.

[29] Griffin MD, Xing N, Kumar R. Vitamin D and its analogs as regulators of immune activation and antigen presentation. *Annu Rev Nutr*. 2003;23:117–145.

[30] McGlade JP, Gorman S, Zosky GR, et al. Suppression of the asthmatic phenotype by ultraviolet B induced, antigen-specific regulatory cells. *Clin Exp Allergy*. 2007;37:1267.

[31] Helming L, Bose J, Ehrchen J, et al. 1α,25-dihydroxyvitamin D3 is a potent suppressor of interferon γ-mediated macrophage activation. *Blood*. 2005;106:4351–4358.

[32] Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr*. 2007;85:788–795.

[33] Devereux G, Litonjua AA, Turner SW, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr*. 2007;85:853–859.

[34] Yadve M, Mittal K. Effect of vitamin D supplementation on moderate to severe bronchial asthma. *Indian J Pediatr*. 2014;81:650–654.
[35] Clifford RL, Knox AJ. Vitamin D: a new treatment for airway remodelling in asthma? *Br J Pharmacol*. 2009;158:1426–1428.
[36] Ginde AA, Mansbach JM, Camargo CA Jr. Vitamin D, respiratory infections, and asthma. *Curr Allergy Asthma Rep*. 2009;9:81–87.
[37] Varney VA, Evans J, Bansal AS. Successful treatment of reactive airways dysfunction syndrome by high-dose vitamin D. *J Asthma Allergy*. 2011;4:87–91.
[38] Hollis BW, Wagner CL, Drezner MK, Binkley NC. Circulating vitamin D (3) and 25 hydroxyvitamin D in humans: an important tool to define adequate nutritional vitamin D status. *J Steroid Biochem Mol Biol*. 2007; 103:631–634.
[39] Taback SP, Simons FE. Anaphylaxis and vitamin D: A role for the sunshine hormone? *J Allergy Clin Immunol*. 2007;120:128–130.
[40] Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr*. 2001;73:288–294.
[41] Lange NE, Litonjua A, Hawrylowicz CM, Weiss S. Vitamin D, the immune system and asthma. *Expert Rev Clin Immunol*. 2009;5:693–702.
[42] Di Rosa M, Malaguarnera M, Nicoletti F, Malaguarnera L. Vitamin D3: a helpful immuno-modulator. *Immunology*. 2011;134:123–139.